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The RECARDINA study protocol: diagnostic utility of ultra-abbreviated echocardiographic protocol for hand-held machines used by non-experts to detect rheumatic heart disease

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Abstract

Introduction

Rheumatic heart disease (RHD) causes significant morbidity and mortality in young people from disadvantaged populations. Early detection through echocardiography screening can facilitate early access to treatment. Large scale implementation of screening could be feasible with the combination of inexpensive standalone ultrasound transducers and upskilling non-expert practitioners to perform abbreviated echocardiography.

Methods and analysis

A prospective cross-sectional study will evaluate an abbreviated echocardiography screening protocol for the detection of latent (asymptomatic) RHD in high-risk populations. The study will evaluate the diagnostic accuracy of health-worker conducted single parasternal-long-axis-view-sweep using handheld (Philips Lumify S4-1 phased array transducer) devices (SPLASH). Each participant will have at least one reference test performed on the same day by an expert echocardiographer. Diagnosis of RHD will be determined by a panel of three experts, using 2012 World Heart Federation criteria.

Sensitivity and specificity of the index test will be calculated with 95% confidence intervals, to determine diagnostic accuracy of a screen-and-refer approach to echocardiography screening for RHD. Remote review of SPLASH images obtained by health-workers will facilitate evaluation of the sensitivity and specificity of an alternative approach, using external review of health-worker obtained SPLASH images to decide onward referral.

Ethics and dissemination

Ethics approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, for the project to be carried out in Timor-Leste (HREC 2019-3399), and in Australia, following review by the Aboriginal Ethics sub-committee (HREC 2019-334). Ethical and technical approval was granted in Timor-Leste, by the Institute National of Health Research Ethics and Technical Committee (1073-MS-INS/GDE/VII/2019).

Study results will be disseminated in the communities involved in the study, and through peer-reviewed publications and conference abstracts.

Trial registration

The study was registered on the Australia New Zealand Clinical Trials Registry (ACTRN12620000122954) prior to completion of recruitment.

Strengths and limitations of this study

- Strengths of the study include:
  - It builds on existing research into the use of hand-held machines by non-experts to detect rheumatic heart disease, using the latest ultrasound technology
  - Non-expert echocardiography will be compared against a reference test (expert echocardiography) performed on the same day
- Limitations include:
  - Reliance on access to high speed internet for image transfer
  - Echocardiography training delivered predominantly in English

Introduction

Rheumatic heart disease (RHD) cripples socioeconomically disadvantaged populations, affecting 33.4 million people worldwide (1). The burden of RHD affecting children who are Indigenous to Australia and Timor-Leste is devastating (2,3). Mild and moderate cases of RHD can occur without apparent symptoms, but progression can result in severe heart disease and early death (4,5). Early detection facilitates treatment. Echocardiography can be used for active case finding in schools and other similar settings, but reliance on expensive machines and highly trained experts are barriers to large-scale implementation (6). Designing and testing simple, cost-effective strategies has the potential to revolutionise early diagnosis and treatment of RHD in resource-limited settings and reduce the impact of morbidity and mortality from this largely preventable disease (7).

The capability of handheld ultrasound machines for RHD screening has been established when operated and interpreted by expert cardiologists (8,9). Utilising non-expert health-workers to perform simplified screening protocols for RHD presents an exciting possibility, given limited access to experts in many settings where RHD is endemic. Recent studies demonstrated diagnostic accuracy of abbreviated echocardiographic screening protocols performed by briefly-trained health-workers and are summarised in Table 1 (10–14).

While abbreviated, protocols requiring multiple views still pose logistical challenges, especially when implemented in non-clinical environments on a large scale. They require the subject to remove all layers of clothing from their upper body, which can compromise privacy and add to discomfort for those undergoing the procedure. In addition, apical views are technically challenging compared to the parasternal-long-axis (PLAX) view, which can be performed relatively easily and rapidly, while preserving the modesty of children and young adults undergoing screening. Recent studies have suggested that PLAX only echocardiography may provide adequate sensitivity for detection of RHD, raising the possibility of using it as a screening test for RHD in high-risk populations, including a study in Timor-Leste which demonstrated sensitivity of 100% (95% confidence interval (CI) 93.0 – 100) for PLAX view echocardiography for detection of RHD, when performed by an expert using a standard portable ultrasound machine (13,15).

Standalone ultrasound devices are now available, which use existing phones and tablets to facilitate handheld echocardiography. They are easy to use and have high fidelity imaging but have limited modalities: 2D and colour Doppler imaging but no spectral Doppler imaging. The availability of these devices makes it imperative to investigate their role in RHD screening, specifically without pulsed wave Doppler, which is currently an integral part of the World Heart Federation guidelines for the echocardiographic diagnosis of RHD (16).

In 2018 we conducted the Pedrino study, training a group of 18 non-expert practitioners from Timor-Leste and Australia using handheld Vscan (Philips, GE Healthcare, USA) devices. Health-workers were trained over a five-day course to perform Single Parasternal Long Axis view with a Sweep using Handheld devices (SPLASH) echocardiography (14). This demonstrated that with brief training (5-day course) health-workers could detect moderate and severe disease (sensitivity 90.6%; 95% CI 75.0 – 98.0) and that further training is required for detection of mild and borderline disease (sensitivity 70.4%; 95% CI 62.2 – 77.8), with some variability between operators (14).

The RECARDINA (Rapid Echocardiography for Congenital And Rheumatic heart Disease – Investigating a New Approach) study has been developed to investigate the diagnostic accuracy and feasibility of health-worker led SPLASH echocardiography for active case finding of RHD, using standalone ultrasound devices (Lumify S4-1 phased array transducer, Philips Healthcare, USA). Given improvements gained through a larger screen, better image resolution and a new, longer training course, we hypothesise that diagnostic accuracy will be improved.

Methods and analysis

Design

A prospective cross-sectional study will be conducted, comparing two approaches to implementation of an abbreviated echocardiography screening protocol performed by briefly-trained non-expert health-workers using standalone ultrasound devices for the detection of latent RHD in high-risk populations. All participants will have at least two echocardiograms performed (one performed by an expert, and the other by a non-expert health-worker) on the same day, and in some cases three (Figure 1).

The first will be a SPLASH echocardiogram performed by a briefly-trained non-expert health-worker with a Lumify S4-1 phased array transducer (Philips Healthcare, USA). If this is considered normal by the health-worker, the second scan will be a SPLASH echocardiogram performed by an expert echocardiographer, also using a Lumify. If either the health-worker or the expert SPLASH echocardiogram is considered abnormal or indeterminate, then the participant will have a full screening echocardiogram performed by an expert echocardiographer on a Vivid I or Q ultrasound machine (GE Healthcare, USA).

The diagnostic accuracy of the health-worker performed SPLASH echocardiogram will be determined by comparing the results of these against the results of the final, expert-performed echocardiogram (full screening echocardiogram for some, expert-performed SPLASH echocardiogram for those who do not require a full screening echocardiogram).

Images stored during the first health-worker performed SPLASH echocardiogram will be reviewed by an expert echocardiographer on a later date, offsite, to elicit any incremental gains in diagnostic accuracy, over and above the real-time determination of the health-worker.

Analysis of these data will allow evaluation of two potential future approaches to scaling up active case finding for RHD, using briefly-trained health-workers to conduct SPLASH echocardiography (Figure 2).

Approach 1 is a two-step screening process, whereby the briefly trained health-worker refers those they deem to have an abnormal or indeterminate SPLASH echocardiogram, for cardiologist review and full diagnostic echocardiogram.

Approach 2 would involve remote expert review of SPLASH images obtained by briefly-trained health-workers, with referral for cardiologist review and full diagnostic echocardiography based on the expert assessment of stored images from the screening SPLASH echocardiogram.

The outcomes of screening will be analysed separately for approaches 1 and 2. The primary outcome is diagnosis of RHD. The sensitivity and specificity of each approach for the detection of RHD will be compared.

Secondary outcomes will be explored for the entire cohort with a final diagnosis of RHD, including time to referral, time to cardiologist review, time to diagnosis and time to commencement of appropriate treatment.

Setting

The study will be conducted in communities in the Dili, Bobonaro and Ermera municipalities of Timor-Leste, and in the 'Top End' region of the Northern Territory of Australia. Timor-Leste has a population of 1.2 million people, a very high burden of RHD (3), and limited access to specialist cardiac services (17,18). The population of the Northern Territory is

approximately 230,000, of whom 26% are Aboriginal or Torres Strait Islander people (19). The disproportionate burden of RHD experienced by Aboriginal and Torres Strait Islander people in Australia is greatest in this part of the country, and predominantly affects people living in small, remote towns (2).

Echocardiography training will be conducted in urban and remote sites in both Timor-Leste and Australia. Echocardiography screening will take place in one urban and two remote sites in Timor-Leste, and two remote sites in Australia. Screening will be conducted in schools, using separate spaces for males and females. Full screening echocardiography, cardiologist consults, counselling and treatment will take place in a separate room.

Echocardiography training

Health-workers undertaking echocardiography training will be expected to complete online modules on the echocardiographic diagnosis of RHD (20), prior to undertaking a two-week training course. Two courses will be conducted, one in Timor-Leste and one in Australia, with between 10-20 health-workers on each course. Health-workers will include Aboriginal Health Practitioners, Registered Nurses, non-specialist doctors, and health-workers without formal qualifications, nominated by local community health centres and hospitals from the locations selected for screening. A subset of those trained will be health-workers who have previously completed brief training using different devices (VScan, GE Healthcare, USA) for the Pedrino study (14).

The courses will comprise lectures and practical training delivered over a total of 10 days; 5 days in an urban site and 5 days in a remote site. Practical training will involve supervised echocardiography with a ratio of tutors to trainees of 1:4, and a mix of subjects. Volunteer children (with healthy hearts and with RHD) will be recruited to attend each day of the training course and will receive repeated echo scans by multiple trainees. Patients who are known by the study investigators to have RHD will be contacted and invited to participate, if written informed consent is provided. All children will have an echocardiogram performed by an expert echocardiographer (sonographer or cardiologist). Any children with evidence of heart disease on echocardiography or on history, will also be offered a formal consultation with a paediatric cardiologist.

In order to successfully complete training, health-workers will be required to perform a minimum of 100 supervised SPLASH studies, pass a written assessment (21 short answer questions, in English) and a practical assessment. Health-workers will be remunerated at their usual rate of pay for the hours of work required. The pass mark on the written assessment is 80%, with opportunity for one re-sit if failed on the first attempt. The practical assessment will involve three supervised SPLASH studies, at least one conducted on a child with an established diagnosis of RHD. The assessment cases will be unknown to the candidates, who will be blinded to any underlying diagnosis. Pre-determined marking criteria will be adjudicated by two assessors. Trainees will need to pass all three studies in order to pass the assessment. If one of the three is failed, the trainee will be able to re-sit the practical assessment, with a further three studies. Those who fail either the written or practical assessment following a re-sit, will not pass the training course and will not be eligible to participate in echocardiography screening for the study.

Study information and consent

Community engagement has occurred with each community group involved in the study. This has occurred through meetings with community leaders, school staff, clinic staff, and in Australia through engagement with local Aboriginal Controlled Community Health Organisations. Conduct of the study will be closely linked to ongoing efforts to work with communities to improve knowledge and understanding of RHD, through development and distribution of locally relevant materials, using local languages.

In each location, information regarding the study will be provided in local languages using verbal communication, flip charts and short videos which include local images and spoken information. Ethical approval to enrol participants without written consent, using an opt-out approach, has been obtained in Timor-Leste. In Australia, all participants require written informed consent to be enrolled. Consent will be obtained from a parent or guardian for those aged less than 18 years; individuals aged 18 years or more will be able to provide consent for themselves.

Inclusion criteria for echocardiographic screening
All children and young people aged between 5 and 20 years present at the school or other screening site on the day of screening will be eligible. Participants are eligible regardless of whether or not they have had a previous echocardiogram or are known to have heart disease.

Exclusion criteria for echocardiographic screening
Children aged under 5 years, and adults aged over 20 years, will be excluded. Participants and their guardians may choose to remove themselves from the study at any time.

Index test
The index test is a SPLASH echocardiogram, conducted by a briefly trained health-worker using a Lumify S4-1 phased array transducer (Philips Healthcare, USA). The health-worker will obtain 2D and colour Doppler images of the mitral and aortic valves, including a sweep in the PLAX plane. Any mitral regurgitation and/or aortic regurgitation will be measured in the longest plane, and the jet length measured in millimetres. All images will be stored as 6-second loops, and still images for jet length measurements.

Any mitral or aortic regurgitation noted on SPLASH echocardiogram will be considered “abnormal” (screen positive). In the absence of any mitral regurgitation or aortic regurgitation or other incidental abnormal findings, the SPLASH echocardiogram will be recorded as “normal” (screen negative). If the SPLASH echocardiogram is assessed as normal, the participant will be referred for a second SPLASH echocardiogram, conducted by an expert echocardiographer. If the SPLASH echocardiogram is assessed by the health-worker as abnormal, or indeterminate, the participant will be referred for a full screening echocardiogram and cardiologist review if this is abnormal (Figure 1).

Reference test for cases not referred for full screening echocardiogram
Participants with an initial SPLASH echocardiogram assessed as normal by the health-worker, will have a second SPLASH echocardiogram immediately, conducted by an expert echocardiographer, using a standalone Lumify transducer (Philips Healthcare, USA). The process of scanning, interpretation and assessment will be the same as for the index test. Participants with a normal SPLASH echocardiogram at this stage will be discharged with a final diagnosis of “no RHD”. Those with abnormal SPLASH echocardiogram (based on any mitral regurgitation, any aortic regurgitation, or any other abnormality detected by the expert sonographer) or an indeterminate SPLASH echocardiogram will be referred for a full expert screening echocardiogram, which will be done immediately using a full capability portable machine (Vivid I or Vivid Q, GE Healthcare) and cardiologist review if this confirms heart disease.

For cases with a normal second SPLASH echocardiogram (conducted by an expert), the second SPLASH echocardiogram outcome will be used as the reference test.

Reference test for cases referred for full screening echocardiogram
For all participants referred for a full screening echocardiogram, this will be used as the reference test. This echocardiogram will be conducted by an expert cardiac sonographer or cardiologist, using a Vivid I or Vivid Q device (GE Healthcare, USA). It will include 2D and

colour Doppler PLAX, parasternal-short-axis, apical 4-chamber and apical 5-chamber views, m-mode continuous and pulse wave interrogation of valves and shunt lesions.

Findings will be reported in real time, and diagnoses of RHD will be made according to World Heart Federation 2012 echocardiographic criteria outlined in Table 2 (16). If any abnormality is identified on the full screening echocardiogram, the participant will have a full anatomic scan to exclude or diagnose congenital heart disease.

Panel review of cases with heart disease
Abnormal cases will be reviewed in real time by a panel of three experts to determine a consensus diagnosis (21). The final diagnoses of RHD will be based on the expert opinion of this panel, who will meet on the same day as screening to review images obtained during the full screening echocardiogram. Cases will be assessed against the World Heart Federation criteria, and a determination of definite or borderline RHD will require agreement from at least two out of three members of the panel (22).

External review of images
All SPLASH echocardiography images that are stored will be transmitted using an encrypted platform and a secure internet connection, for review by an expert paediatric cardiologist or cardiac sonographer with experience in paediatric RHD screening studies. Any mitral or aortic regurgitation noted on SPLASH echo will be considered “abnormal”. The longest length (cm) of the mitral or aortic regurgitation jet will be measured. Detection of morphological valve changes or other abnormalities will also warrant a decision to label the echo “abnormal”. In the absence of any of these findings, and if the images obtained are adequate, the SPLASH echocardiogram will be assessed as normal. The expert reviewer will also record whether a diagnosis of definite or borderline RHD is suspected on the basis of the SPLASH echo images they have to review. They will also make an assessment of the adequacy of the images, using a simple rating scale consisting of “adequate”, “poor quality but assessment made”, and “not interpretable”.

Any cases that are found to be abnormal on external review of SPLASH images, that have not already been referred for a full screening echocardiogram and cardiologist review as required, will be referred following this review.

Sample size calculation
Sample size was calculated assuming a combined prevalence of definite and borderline RHD of 2.5%, which is a conservative estimate based on previous studies (2,3). Using formulae for calculation of sample size for evaluation of diagnostic tests, to demonstrate 95% sensitivity of the SPLASH protocol using study Approach 1, with precision of 0.05, a sample size of 2920 is required (23). Based on population size, and recruitment success in previous studies, we anticipate that it will be feasible to recruit between 2000 – 3000 participants in Timor-Leste, and between 500 – 1000 participants in Australian sites.

Data management and analysis
Echocardiography images will be stored on a on a secure server (Synapse, Fujifilm, Japan)) hosted by NT Cardiac in Darwin, Australia. Other study data will be collected using a REDCap 8.7.4 (Vanderbilt University, USA) database hosted at Menzies School of Health Research (Darwin, Australia) (24). Statistical analysis will be conducted using STATA 15.1 (StataCorp, USA). The reason for missing data will be recorded; missing data will not be imputed.

For statistical analysis, the final diagnosis will be based on the findings of the final expert echocardiogram performed (SPLASH or full screening study), using the panel decision if a panel was convened (if the echocardiogram was abnormal), or using the expert decision if no panel was needed (because the echocardiogram was normal).

Primary analysis will involve calculation of sensitivity, specificity and likelihood ratios for both Approach 1 and Approach 2. For approach 1, SPLASH echocardiogram result of abnormal or normal, as reported by briefly trained health-workers, will be compared against the definitive final diagnosis based on reference test or panel. For approach 2, SPLASH echocardiogram performed by briefly-trained health-worker and interpreted by a remote expert will be compared with the definitive final diagnosis based on reference test or panel.

Median time to referral, time to diagnosis, and time to commencement of appropriate management will be reported for the cohort of patients with newly diagnosed RHD.

SPLASH echocardiography findings from the briefly trained health-workers will also be directly compared against findings from the external expert review of deidentified SPLASH echocardiogram images, with calculation of diagnostic agreement using Cohen's kappa coefficient and reported with a 95% CI.

A random selection of 10% of full diagnostic echocardiograms completed at cardiologist review will be also reviewed by a blinded expert paediatric cardiologist, and the diagnostic agreement regarding RHD diagnosis will be calculated using Cohen's kappa coefficient and reported with a 95% confidence interval.

The prevalence of congenital heart disease and RHD (borderline and definite cases) will be estimated and described with 95% confidence intervals for the overall screened population and for relevant sub-groups (divided by age, gender and geographical location), recognising that SPLASH echocardiography may not detect all cases of congenital heart disease. The impact of potential demographic risk factors will be described using univariate and multivariate analyses, to obtain adjusted odds ratios for any significant variables. Results of analyses will be considered significant if the p value < 0.05.

Follow-up of cases

Any participant with a final diagnosis that meets World Heart Federation criteria for borderline or definite RHD (Figure 2) or congenital heart disease will be counselled by a clinician or clinical team, along with their parent or guardian, based on the final panel diagnosis. All cases of borderline or definite RHD will receive education and counselling about the diagnosis, its management, and prevention of further progression of disease by trained health-workers, using local languages where appropriate. These cases will also be recorded on an RHD register, either the Northern Territory RHD Register (in Australia) or the Maluk Timor RHD Register (in Timor-Leste), to facilitate ongoing follow-up and management.

Those with a new diagnosis of definite RHD will be commenced as soon as possible on regular 4-weekly long acting penicillin injections as secondary prophylaxis, if they are not receiving this already. This is expected to occur within one week of screening. Any cases of RHD or congenital heart disease that may warrant surgical intervention, will be referred for consideration for surgery in Australia. Cases of borderline RHD will be referred for a paediatric review which will be conducted at the local health clinic, during the week of screening, to determine whether ongoing penicillin prophylaxis or another course of management is required. All participants with borderline or definite RHD will be followed up with at least one echocardiogram (one to two years after screening) by the study team, with further cardiology and echocardiography follow up arranged through local health services, with monitoring of follow up conducted through the normal processes of the relevant RHD Register.

Ethics and dissemination

The RECARDINA study received ethical approval from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, initially for the project to be carried out in Timor-Leste (HREC 2019-3399), and subsequently for implementation in Australia, following review by the Aboriginal Ethics sub-committee (HREC 2019-334). Ethical and technical approval was also granted in Timor-Leste, by the Institute National of Health Research Ethics and Technical Committee (1073-MS-INS/GDE/VII/2019).

The study was registered on the Australia New Zealand Clinical Trials Registry (ACTRN12620000122954) prior to completion of recruitment.

Individual participant level results will be communicated, with consent, to relevant clinical services to ensure ongoing follow-up as required.

Investigators have committed to disseminating aggregate results of the study to communities involved in the study, both for training and screening. This will occur with verbal and written summaries, presented to community leaders, schools, and clinical services. A summary of results will be presented in written form (English and Tetum) to the Ministry of Health in Timor-Leste, and to the Institute National Health. All data in these reports will be deidentified, and presented in aggregate form, to ensure anonymity of participants.

Findings will also be presented at national and international scientific meetings, and in peer-reviewed publications. The focus of these presentations will be on the diagnostic accuracy of the new approach to echocardiography screening, and will also include prevalence data obtained through screening.

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Table 1: Abbreviated echocardiography screening protocols for rheumatic heart disease utilising non-expert technicians

Study	**Mirabel, 2014** (10)	**Engelman, 2016** (11)	**Ploutz, 2016** (12)	**Diamantino, 2018** (13)	**Francis, 2018** (14)
Setting	New Caledonia	Fiji	Uganda	Uganda / Brazil	Timor-Leste / Australia
Age of participants	9-10 years	5-15 years	5-17 years	7-18 years	5-20 years
Sample size	1217	2004	956	587	2574
Design	Prospective	Prospective	Prospective	Retrospective	Prospective
Echo machine	Handheld (GE Vscan)	Portable (SonoSite M-Turbo)	Handheld (GE Vscan)	Handheld (GE Vscan)	Handheld (GE Vscan)
Echo protocol	PLAX, PSAX, apical views	PLAX, PSAX, apical views	PLAX, apical views	Single PLAX view	Single PLAX view
Diagnostic criteria:	MR > 2cm or any AR	Any MR or any AR	MR > 1.5cm or any AR	MR > 1.5cm or any AR	Any MR or any AR
Training	3 days lectures; 30 hours supervised practical sessions	Online modules; 8-week course including theory and practical sessions	2.5-day course including theory and practical sessions; participants had previous echo training	12 – 18 months of practical experience^	Online modules; 5-day course including theory and practical sessions
RHD cases	15 definite, 34 borderline	14 definite, 43 borderline	11 definite, 32 borderline	76 definite, 122 borderline	55 definite, 47 borderline
Prevalence of any RHD	4.0%	2.8%	4.5%	N/A*	4.1%
Sensitivity (95% CI) for any RHD:	83.7 (70.7 – 91.6)	84.2 (72.1 – 92.5)	74.4 (58.8 – 86.5)	85 (80 - 90)	70.4 (62.2 – 77.8)
Specificity (95% CI) for any RHD:	90.9 (89.9 – 92.4)	85.6 (83.9 – 87.1)	78.8 (76.0 – 81.4)	65 (60 - 70)	78.1 (76.4 – 79.8)

^ Echocardiography was performed by experts; 12-18 months training relates to those who interpreted the images

*retrospective review of a selected cohort

Table 2: 2012 World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease in people aged 20 years or less (16).

Definite RHD (either A, B, C, or D): A) Pathological MR and at least two morphological features of RHD of the MV B) MS mean gradient ≥4 mmHg* C) Pathological AR and at least two morphological features of RHD of the AV‡ D) Borderline disease of both the AV and MV§
Borderline RHD (either A, B, or C): A) At least two morphological features of RHD of the MV without pathological MR or MS B) Pathological MR C) Pathological AR
Normal echocardiographic findings (all of A, B, C, and D): A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR) B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR) C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
* Congenital MV anomalies must be excluded. ‡ Bicuspid AV, dilated aortic root, and hypertension must be excluded. § Combined AR and MR in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic. Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease; WHF, World Heart Federation.

Authors contributions: JRF and HF conceived the study and wrote initial drafts of the protocol; GAW, AK, APR, JY, JC, VW, AM, BR contributed to study design and reviewed and approved the written protocol; VW provided input on issues related to engagement with Aboriginal and Torres Strait Islander people; and AM provided input on issues related to engaging with Timorese people and the health system in Timor-Leste.

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Competing interests statement: None of the authors have competing interests to declare.

Patient and public involvement statement: People living in communities that have been involved in previous similar research that we have conducted, were invited to provide feedback on the research and to make suggestions for further studies. Health-worker who had received training in handheld echocardiography were also specifically asked for their perspectives on the training and echocardiography screening, and suggest improvements to both, for inclusion in this study protocol. Public engagement in study design commenced in 2018, and continued until the date of ethics submission. Feedback was obtained specifically in relation to inclusion of Aboriginal health workers, and appropriateness of models of care involving echocardiography screening and onward referral. Consent information was developed in collaboration with members of the public, and supplemented by additional educational material regarding rheumatic heart disease, developed in local languages. We have committed to disseminating results in the communities involved, prior to wider dissemination and publication.

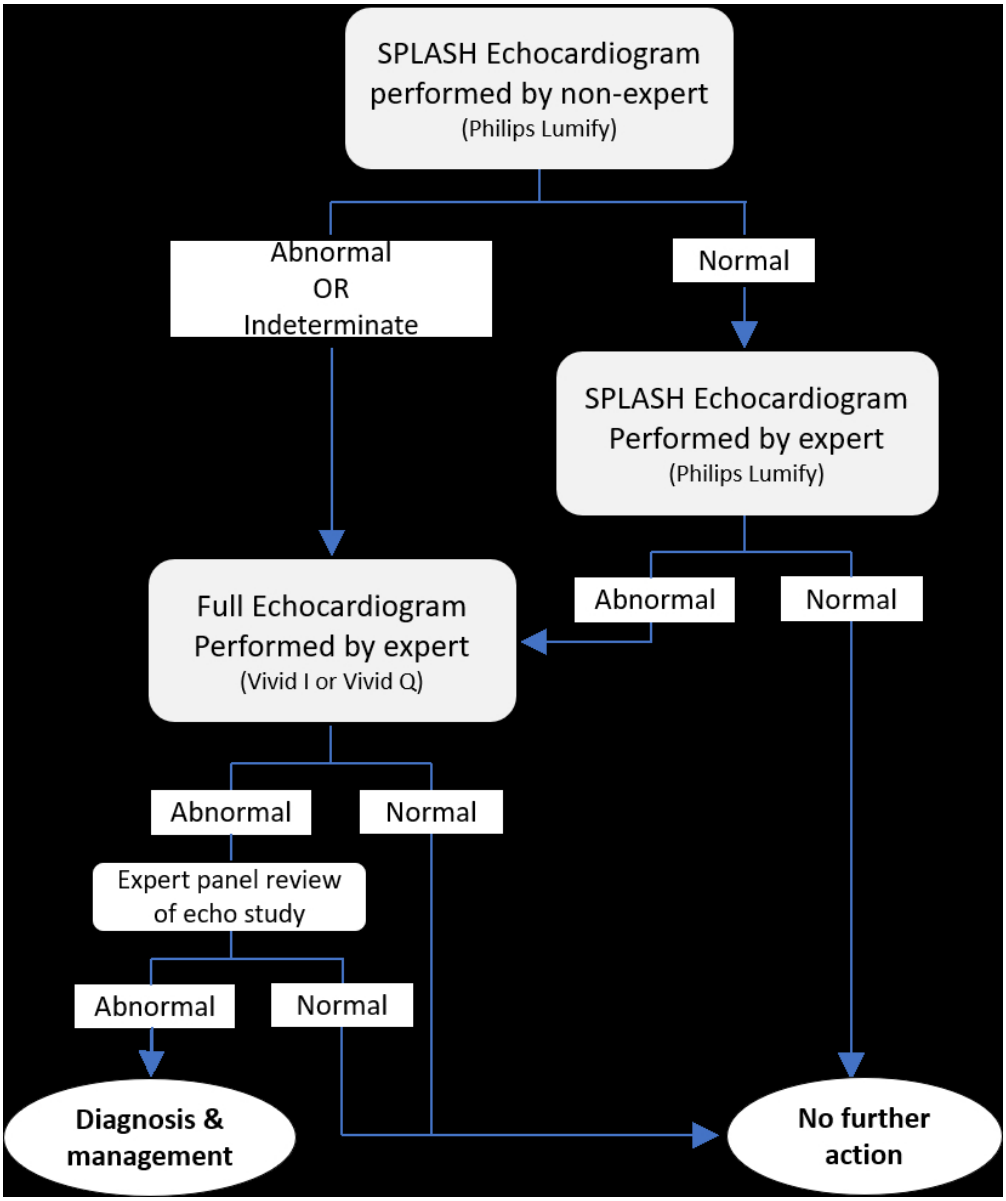

Figure 1: Flow of participants through the study

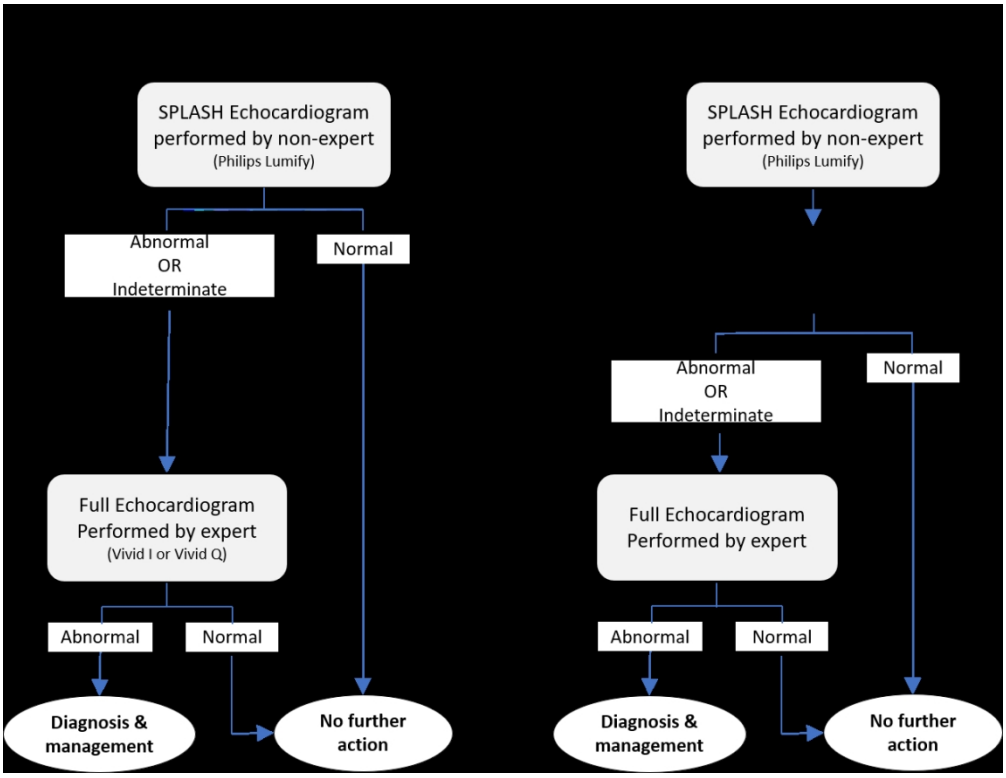

Figure 2: Illustration of Approach 1 and Approach 2

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	
	4	Study objectives and hypotheses	
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	
Participants	**6**	Eligibility criteria	
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	
	8	Where and when potentially eligible participants were identified (setting, location and dates)	
	9	Whether participants formed a consecutive, random or convenience series	
Test methods	**10a**	Index test, in sufficient detail to allow replication	
	10b	Reference standard, in sufficient detail to allow replication	
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	
	15	How indeterminate index test or reference standard results were handled	
	16	How missing data on the index test and reference standard were handled	
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/A
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/A
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	N/A
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	9
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	16

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

The RECARDINA study protocol: diagnostic utility of ultra-abbreviated echocardiographic protocol for hand-held machines used by non-experts to detect rheumatic heart disease

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Valvular heart disease < CARDIOLOGY, Paediatric cardiology < PAEDIATRICS, PUBLIC HEALTH

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The RECARDINA study protocol: diagnostic utility of ultra-abbreviated echocardiographic protocol for hand-held machines used by non-experts to detect rheumatic heart disease

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Abstract

Introduction

Rheumatic heart disease (RHD) causes significant morbidity and mortality in young people from disadvantaged populations. Early detection through echocardiography screening can facilitate early access to treatment.Large scale implementation of screening could be feasible with the combination of inexpensive standalone ultrasound transducers and upskilling non-expert practitioners to perform abbreviated echocardiography.

Methods and analysis

A prospective cross-sectional study will evaluate an abbreviated echocardiography screening protocol for the detection of latent (asymptomatic) RHD in high-risk populations. The study will evaluate the diagnostic accuracy of health-worker conducted single parasternal-long-axis-view-sweep usinghandheld (Philips Lumify S4-1 phased array transducer) devices(SPLASH). Each participant will have at least one reference test performed on the same day by an expert echocardiographer. Diagnosis of RHD will be determined by a panel of three experts, using 2012 World Heart Federation criteria.

Sensitivity and specificity of the index test will be calculated with 95% confidence intervals, to determine diagnostic accuracy of a screen-and-refer approach to echocardiography screening for RHD. Remote review of SPLASH images obtained by health-workers will facilitate evaluation of the sensitivity and specificity of an alternative approach, using external review of health-worker obtained SPLASH images to decide onward referral.

Ethics and dissemination

Ethics approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, for the project to be carried out in Timor-Leste (HREC 2019-3399), and in Australia, following review by the Aboriginal Ethics sub-committee (HREC 2019-334). Ethical and technical approval was granted in Timor-Leste, by the Institute National of Health Research Ethics and Technical Committee (1073-MS-INS/GDE/VII/2019).

Study results will be disseminated in the communities involved in the study, and through peer-reviewed publications and conference abstracts.

Trial registration

The study was registered on the Australia New Zealand Clinical Trials Registry (ACTRN12620000122954) prior to completion of recruitment.

Strengths and limitations of this study

- Strengths of the study include:
  - It builds on existing research into the use of hand-held machines by non-experts to detect rheumatic heart disease, using the latest ultrasound technology
  - Non-expert echocardiography will be compared against a reference test (expert echocardiography) performed on the same day
- Limitations include:
  - Reliance on access to high speed internet for image transfer
  - Echocardiography training delivered predominantly in English

Introduction

Rheumatic heart disease (RHD) cripples socioeconomically disadvantaged populations, affecting 33.4 million people worldwide(1). The burden of RHDaffecting children who are Indigenous to Australia and Timor-Leste is devastating (2,3). Mild and moderate cases of RHD can occur without apparent symptoms, but progression can result in severe heart disease and early death(4,5). Early detection facilitates treatment. Echocardiographycan be used for active case finding in schools and other similar settings, but reliance on expensive machines and highly trained experts are barriers to large-scale implementation(6). Designing and testing simple, cost-effective strategies has the potential to revolutionise early diagnosis and treatment of RHD in resource-limited settings and reduce the impact of morbidity and mortality from this largely preventable disease (7).

The capability of handheld ultrasound machines for RHD screening has been established when operated and interpreted by expert cardiologists(8,9). Utilising non-expert health-workers to perform simplified screening protocols for RHD presents an exciting possibility, given limited access to experts in many settings where RHD is endemic. Recent studies demonstrated diagnostic accuracy of abbreviated echocardiographic screening protocols performed by briefly-trained health-workers and are summarised in Table 1 (10–14).

While abbreviated, protocols requiring multiple views still pose logistical challenges, especially when implemented in non-clinical environments on a large scale. They require the subject to remove all layers of clothing from their upper body, which can compromise privacy and add to discomfort for those undergoing the procedure. In addition, apical views are technically challenging compared to the parasternal-long-axis (PLAX) view, which can be performed relatively easily and rapidly, while preserving the modesty of children and young adults undergoing screening.Recent studies have suggested that PLAX only echocardiography may provide adequate sensitivity for detection of RHD, raising the possibility of using it as a screening test for RHD in high-risk populations, including a study in Timor-Leste which demonstrated sensitivity of 100% (95% confidence interval (CI) 93.0 – 100) for PLAX view echocardiography for detection of RHD, when performed by an expert using a standard portable ultrasound machine(13,15).

Standalone ultrasound devices are now available, which use existing phones and tablets to facilitate handheld echocardiography. They are easy to use and have high fidelity imaging but have limited modalities: 2D and colour Doppler imaging but no spectral Doppler imaging. The availability of these devices makes it imperative to investigate their role in RHD screening, specifically without pulsed wave Doppler, which is currently an integral part of the World Heart Federationguidelines for the echocardiographic diagnosis of RHD (16).

In 2018 we conducted the Pedrino study, training a group of 18 non-expert practitioners from Timor-Leste and Australia using handheld Vscan (Philips, GE Healthcare, USA) devices. Health-workers were trained over a five-day course to perform Single Parasternal Long Axis view with a Sweep using Handheld devices (SPLASH) echocardiography (14). This demonstrated that with brief training (5-day course) health-workers could detect moderate and severe disease (sensitivity 90.6%; 95%CI 75.0 – 98.0) and that further training is required for detection of mild and borderline disease (sensitivity 70.4%; 95% CI 62.2 – 77.8), with some variability between operators(14).

The RECARDINA (Rapid Echocardiography for Congenital And Rheumatic heart Disease – Investigating a New Approach) study has been developed to investigate the diagnostic accuracy and feasibility of health-worker led SPLASH echocardiography for active case finding of RHD, using standalone ultrasound devices (Lumify S4-1 phased array transducer, Philips Healthcare, USA). Given improvements gained through a larger screen, better image resolution and a new, longertraining course, we hypothesise that diagnostic accuracy will be improved.

Methods and analysis

Design

A prospective cross-sectional study will be conducted, comparing two approaches to implementation of an abbreviated echocardiography screening protocol performed by briefly-trained non-expert health-workers using standalone ultrasounddevices for the detection of latent RHD in high-risk populations. All participants will have at least two echocardiograms performed (one performed by an expert, and the other by a non-expert health-worker) on the same day, and in some cases three (Figure 1).

The first will be a SPLASH echocardiogram performed by a briefly-trained non-expert health-worker with a Lumify S4-1 phased array transducer (Philips Healthcare, USA). If this is considered normal by the health-worker, the second scan will be a SPLASH echocardiogram performed by an expert echocardiographer, also using a Lumify. If either the health-worker or the expert SPLASH echocardiogram is considered abnormal or indeterminate, then the participant will have afull screening echocardiogram performed by an expert echocardiographer on a Vivid I or Q ultrasound machine (GE Healthcare, USA).

The diagnostic accuracy of the health-worker performed SPLASH echocardiogram will be determined by comparing the results of these against the results of the final, expert-performed echocardiogram (full screening echocardiogram for some, expert-performed SPLASH echocardiogram for those who do not require a full screening echocardiogram).

Images stored during the first health-worker performed SPLASH echocardiogram will be reviewed by an expert echocardiographer on a later date, offsite, to elicit any incremental gains in diagnostic accuracy, over and above the real-time determination of the health-worker.

Analysis of these data will allow evaluation of two potential future approaches to scaling up active case finding for RHD, using briefly-trained health-workers to conduct SPLASH echocardiography (Figure 2).

Approach 1 is a two-step screening process, whereby the brieflytrained health-workerrefers those they deem to have an abnormal or indeterminate SPLASH echocardiogram, for cardiologist review and full diagnostic echocardiogram.

Approach 2 would involve remote expert review of SPLASH images obtained by briefly-trained health-workers, with referral for cardiologist review and full diagnostic echocardiography based on the expert assessment of stored images from the screening SPLASH echocardiogram.

The outcomes of screening will be analysed separately for approaches 1 and 2. The primary outcome is diagnosis of RHD.The sensitivity and specificity of each approach for the detection of RHD will be compared.

Secondary outcomes will be explored for the entire cohort with a final diagnosis of RHD, including time to referral, time to cardiologist review, time to diagnosis and time to commencement of appropriate treatment.

Setting

The study will be conducted in communities in the Dili, Bobonaro and Ermera municipalities of Timor-Leste, and in the ‘Top End’ region of the Northern Territory of Australia. Timor-Leste has a population of 1.2 million people, a very high burden of RHD (3), and limited access to specialist cardiac services (17,18). The population of the Northern Territory

isapproximately 230,000, of whom 26% are Aboriginal or Torres Strait Islander people(19). The disproportionate burden of RHD experienced by Aboriginal and Torres Strait Islander people in Australia is greatest in this part of the country, and predominantly affects people living in small, remote towns (2).

Echocardiography training will be conducted in urban and remote sites in both Timor-Leste and Australia. Echocardiography screening will take place in one urban and two remote sites in Timor-Leste, and two remote sites in Australia. Screening will be conducted in schools, using separate spaces for males and females. Full screening echocardiography, cardiologist consults, counselling and treatment will take place in a separate room.

Echocardiography training

Health-workers undertaking echocardiography training will be expected to complete online modules on the echocardiographic diagnosis of RHD(20), prior to undertaking a two-week training course.Two courses will be conducted, one in Timor-Leste and one in Australia, with between 10-20 health-workers on each course. Health-workers will include Aboriginal Health Practitioners, Registered Nurses, non-specialist doctors, and health-workers without formal qualifications, nominated by local community health centres and hospitals from the locations selected for screening. A subset of those trained will be health-workers who have previously completed brief training using different devices (VScan, GE Healthcare, USA) for the Pedrino study (14).

The courses will comprise lectures and practical training delivered over a total of 10 days; 5 days in an urban site and 5 days in a remote site. Practical training will involve supervised echocardiography with a ratio of tutors to trainees of 1:4, and a mix of subjects.Volunteer children (with healthy hearts and with RHD) will be recruited to attend each day of the training course and will receive repeated echo scans by multiple trainees. Patients who are known by the study investigators to have RHD will be contacted and invitedto participate, if written informed consent is provided. All children will have an echocardiogram performed by an expert echocardiographer (sonographer or cardiologist). Any children with evidence of heart disease on echocardiography or on history, will also be offered a formal consultation with a paediatric cardiologist.

In order to successfully complete training, health-workers will be required to perform a minimum of 100 supervised SPLASH studies, pass a written assessment (21 short answer questions, in English) and a practical assessment. Health-workers will be remunerated at their usual rate of pay for the hours of work required. The pass mark on the written assessment is 80%, with opportunity for one re-sit if failed on the first attempt. The practical assessment will involve three supervised SPLASH studies, at least one conducted on a child with an established diagnosis of RHD.The assessment cases will be unknown to the candidates, who will be blinded to any underlying diagnosis. Pre-determined marking criteria will be adjudicated by two assessors. Trainees will need to pass all three studies in order to pass the assessment. If one of the three is failed, the trainee will be able to re-sit the practical assessment, with a further three studies. Those who fail either the written or practical assessment following a re-sit, will not pass the training course and will not be eligible to participate in echocardiography screening for the study.

Study information and consent

Community engagement has occurred with each community group involved in the study. This has occurred through meetings with community leaders, school staff, clinic staff, and in Australia through engagement with local Aboriginal Controlled Community Health Organisations. Conduct of the study will be closely linked to ongoing efforts to work with communities to improve knowledge and understanding of RHD, through development and distribution of locally relevant materials, using local languages.

In each location, information regarding the study will be provided in local languages using verbal communication, flip charts and short videos which include local images and spoken information. Ethical approval to enrol participants without written consent, using an opt-out approach, has been obtained in Timor-Leste. In Australia, all participants require written informed consent to be enrolled. Consent will be obtained from a parent or guardian for those aged less than 18 years; individuals aged 18 years or more will be able to provide consent for themselves.

Inclusion criteria for echocardiographic screening
All children and young people aged between 5 and 20 years present at the school or other screening site on the day of screening will be eligible.Participants are eligible regardless of whether or not they have had a previous echocardiogram or are known to have heart disease.

Exclusion criteria for echocardiographic screening
Children aged under 5 years, and adults aged over 20 years,will be excluded. Participants and their guardians may choose to remove themselves from the study at any time.

Index test
The index test is a SPLASH echocardiogram, conducted by a briefly trained health-worker using a Lumify S4-1 phased array transducer (Philips Healthcare, USA). The health-worker will obtain 2D and colour Doppler images of the mitral and aortic valves, including a sweep in the PLAX plane. Any mitral regurgitation and/or aortic regurgitation will be measured in the longest plane, and the jet length measured in millimetres. All images will be stored as 6-second loops, and still images for jet length measurements.

Any mitral or aortic regurgitation noted on SPLASH echocardiogram will be considered “abnormal” (screen positive). In the absence of any mitral regurgitation or aortic regurgitation or other incidental abnormal findings, the SPLASH echocardiogram will be recorded as “normal” (screen negative). If the SPLASH echocardiogram is assessed as normal, the participant will be referred for a second SPLASH echocardiogram, conducted by an expert echocardiographer. If the SPLASH echocardiogram is assessed by the health-workeras abnormal, or indeterminate, the participant will be referred for a full screening echocardiogramand cardiologist review if this is abnormal (Figure 1).

Reference test for cases not referred for full screening echocardiogram
Participants with an initial SPLASH echocardiogram assessed as normal by the health-worker, will have a second SPLASH echocardiogram immediately, conducted by an expert echocardiographer, using a standalone Lumify transducer(Philips Healthcare, USA). The process of scanning, interpretation and assessment will be the same as for the index test. Participants with a normal SPLASH echocardiogram at this stage will be discharged with a final diagnosis of “no RHD”. Those with abnormal SPLASH echocardiogram (based on any mitral regurgitation, any aortic regurgitation, or any other abnormality detected by the expert sonographer) or an indeterminate SPLASH echocardiogramwill be referred for a full expert screening echocardiogram, which will be done immediatelyusing a full capability portable machine (Vivid I or Vivid Q, GE Healthcare) and cardiologist review if this confirms heart disease.

For most cases with a normal second SPLASH echocardiogram (conducted by an expert), the second SPLASH echocardiogram outcome will be used as the reference test. At selection of cases with normal findings on both SPLASH echocardiograms will also have a full screening echocardiogram, which will be used as the reference test in these cases.

Reference test for cases referred for full screening echocardiogram

For all participants referred for a full screening echocardiogram, this will be used as the reference test. This echocardiogram will be conducted by an expert cardiac sonographer or cardiologist, using a Vivid I or Vivid Q device (GE Healthcare, USA). It will include 2D and colour Doppler PLAX, parasternal-short-axis, apical 4-chamber and apical 5-chamber views, m-mode continuous and pulse wave interrogation of valves and shunt lesions.

Findings will be reported in real time, and diagnoses of RHD will be made according to World Heart Federation 2012 echocardiographic criteria outlined in Table 2(16). If any abnormality is identified on the full screening echocardiogram, the participant will have a full anatomic scan to exclude or diagnose congenital heart disease.

Panel review of cases with heart disease

All abnormal cases will be reviewed in real time by a panel of three experts to determine a consensus diagnosis (21).Experts will also be encouraged to request a panel in cases that are deemed normal, if there are findings that could be seen in borderline or definite RHD. The final diagnoses of RHD will be based on the expert opinion of this panel, who will meet on the same day as screening to review images obtained during the full screening echocardiogram. Cases will be assessed against the World Heart Federation criteria, and a determination of definite or borderline RHD will require agreement from at least two out of three members of the panel (22).

External review of images

All SPLASH echocardiography images that are stored will be transmitted using an encrypted platform and a secure internet connection, for review by an expert paediatric cardiologist or cardiac sonographer with experience in paediatric RHD screening studies. Any mitral or aortic regurgitation noted on SPLASH echo will be considered “abnormal”. The longest length (cm) of themitral or aortic regurgitation jet will be measured. Detection of morphological valve changes or other abnormalities will also warrant a decision to label the echo “abnormal”. In the absence of any of these findings, and if the images obtained are adequate, the SPLASH echocardiogram will be assessed as normal. The expert reviewer will also record whether a diagnosis of definite or borderline RHD is suspected on the basis of the SPLASH echo images they have to review. They will also make an assessment of the adequacy of the images, using a simple rating scale consisting of “adequate”, “poor quality but assessment made”, and “not interpretable”.

Any cases that are found to be abnormal on external review of SPLASH images, that have not already been referred for a full screening echocardiogram and cardiologist review as required, will be referred following this review.

Sample size calculation

Sample size was calculated assuming a combined prevalence of definite and borderline RHD of 2.5%, which is a conservative estimate based on previous studies (2,3).Using formulae for calculation of sample size for evaluation of diagnostic tests,to demonstrate 95% sensitivity of the SPLASH protocol using study Approach 1, with precision of 0.05, a sample size of 2920 is required (23). Based on population size, and recruitment success in previous studies, we anticipate that it will be feasible to recruit between 2000 – 3000 participants in Timor-Leste, and between 500 – 1000 participants in Australian sites.

Data management and analysis

Echocardiography images will be stored on a on a secure server (Synapse, Fujifilm, Japan) hosted by NT Cardiac in Darwin, Australia. Other study data will be collected using a REDCap 8.7.4 (Vanderbilt University, USA) database hosted at Menzies School of Health Research (Darwin, Australia)(24). Statistical analysis will be conducted using STATA 15.1 (StataCorp, USA). The reason for missing data will be recorded; missing data will not be imputed.

For statistical analysis, the final diagnosis will be based on the findings of the final expert echocardiogram performed (SPLASH or full screening study), using the panel decision if a panel was convened (if the echocardiogram was abnormal), or using the expert decision if no panel was needed (because the echocardiogram was normal).

Primary analysis will involve calculation of sensitivity, specificity and likelihood ratios for both Approach 1 and Approach 2. For approach 1, SPLASH echocardiogramresult of abnormal or normal, as reported by briefly trained health-workers, will be compared against the definitive final diagnosis based on reference test or panel. For approach 2, SPLASHechocardiogram performed by briefly-trained health-worker and interpreted by a remote expert will be compared with the definitive final diagnosis based on reference test or panel.

Sensitivity and negative predictive values will also be calculated separately for specific categories of RHD diagnosis that are at higher risk of progression, including moderate and severe cases (25), and those with a risk score >= 10 based on the scoring system proposed by Nunes et al (26).

Median time to referral, time to diagnosis, and time to commencement of appropriate management will be reported for the cohort of patients with newly diagnosed RHD.

SPLASH echocardiography findings from the briefly trained health-workers will also be directly compared against findings from the external expert review of deidentified SPLASH echocardiogram images, with calculation of diagnostic agreement using Cohen's kappa coefficient and reported with a 95% CI.

A random selection of 10% of full diagnostic echocardiograms completed at cardiologist review will be also reviewed by a blinded expert paediatric cardiologist, and the diagnostic agreement regarding RHD diagnosis will be calculated using Cohen's kappa coefficient and reported with a 95% confidence interval.

The prevalence of congenital heart disease and RHD (borderline and definite cases) will be estimated and described with 95% confidence intervals for the overall screened population and for relevant sub-groups (divided by age, gender and geographical location), recognising that SPLASH echocardiography may not detect all cases of congenital heart disease. The impact of potential demographic risk factors will be described using univariate and multivariate analyses, to obtain adjusted odds ratios for any significant variables. Results of analyses will be considered significant if the p value < 0.05.

Follow-up of cases

Any participant with a final diagnosis that meets World Heart Federation criteria for borderline or definite RHD (Figure 2) or congenital heart disease will be counselled by a clinician or clinical team, along with their parent or guardian, based on the final panel diagnosis. All cases of borderline or definite RHD will receive education and counselling about the diagnosis, its management, and prevention of further progression of diseaseby trained health-workers, using local languages where appropriate. These cases will also be recorded on an RHD register, either the Northern Territory RHD Register (in Australia) or the Maluk Timor RHD Register (in Timor-Leste), to facilitate ongoing follow-up and management.

Those with a new diagnosis of definite RHD will be commenced as soon as possible on regular 4-weekly long acting penicillin injections as secondary prophylaxis, if they are not receiving this already, based on Australian guidelines, which recommend secondary prophylaxis for echocardiography-detected definite RHD (27), pending the results of ongoing research into the impact of secondary prophylaxis on progression of sub-clinical RHD (28).

This is expected to occur within one week of screening. Any cases of RHD or congenital heart disease that may warrant surgical intervention, will be referred for consideration for surgery in Australia. Cases of borderline RHD will be referred for a paediatric review which will be conducted at the local health clinic, during the week of screening, to determine whether ongoing penicillin prophylaxis or another course of management is required. All participants with borderline or definite RHD will be followed up with at least one echocardiogram (one to two years after screening) by the study team, with further cardiology and echocardiography follow up arranged through local health services, with monitoring of follow up conducted through the normal processes of the relevant RHD Register.

Patient and public involvement statement

People living in communities that have been involved in previous similar research that we have conducted, were invited to provide feedback on the research and to make suggestions for further studies. Health-worker who had received training in handheld echocardiography were also specifically asked for their perspectives on the training and echocardiography screening, and suggest improvements to both, for inclusion in this study protocol. Public engagement in study design commenced in 2018, and continued until the date of ethics submission. Feedback was obtained specifically in relation to inclusion of Aboriginal health workers, and appropriateness of models of care involving echocardiography screening and onward referral. Consent information was developed in collaboration with members of the public, and supplemented by additional educational material regarding rheumatic heart disease, developed in local languages. We have committed to disseminating results in the communities involved, prior to wider dissemination and publication.

Ethics and dissemination

The RECARDINA study received ethical approval from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, initially for the project to be carried out in Timor-Leste (HREC 2019-3399), and subsequently for implementation in Australia, following review by the Aboriginal Ethics sub-committee (HREC 2019-334). Ethical and technical approval was also granted in Timor-Leste, by the Institute National of Health Research Ethics and Technical Committee (1073-MS-INS/GDE/VII/2019).

The study was registered on the Australia New Zealand Clinical Trials Registry (ACTRN12620000122954) prior to completion of recruitment.

Individual participant level results will be communicated, with consent, to relevant clinical services to ensure ongoing follow-up as required.

Investigators have committed to disseminatingaggregate results of the study to communities involved in the study, both for training and screening. This will occur with verbal and written summaries, presented to community leaders, schools, and clinical services. A summary of results will be presented in written form (English and Tetum) to the Ministry of Health in Timor-Leste, and to the Institute National Health. All data in these reports will be deidentified, and presented in aggregate form, to ensure anonymity of participants.

Findings will also be presented at national and international scientific meetings, and in peer-reviewed publications. The focus of these presentations will be on the diagnostic accuracy of the new approach to echocardiography screening, and will also include prevalence data obtained through screening.

Figure 1: Flow of participants through the study

Figure 2: Illustration of Approach 1 and Approach 2

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Table 1: Abbreviated echocardiography screening protocols for rheumatic heart disease utilising non-expert technicians

Study	**Mirabel, 2014** (10)	**Engelman, 2016**(11)	**Ploutz, 2016**(12)	**Diamantino, 2018**(13)	**Francis, 2018**(14)
Setting	New Caledonia	Fiji	Uganda	Uganda/Brazil	Timor-Leste /Australia
Age of participants	9-10 years	5-15 years	5-17 years	7-18 years	5-20 years
Sample size	1217	2004	956	587	2574
Design	Prospective	Prospective	Prospective	Retrospective	Prospective
Echo machine	Handheld(GE Vscan)	Portable (SonoSite M-Turbo)	Handheld (GE Vscan)	Handheld (GE Vscan)	Handheld (GE Vscan)
Echo protocol	PLAX, PSAX, apical views	PLAX, PSAX, apical views	PLAX, apical views	Single PLAX view	Single PLAX view
Diagnostic criteria:	MR >2cm or any AR	Any MR or any AR	MR >1.5cm or any AR	MR >1.5cm or any AR	Any MR or any AR
Training	3 dayslectures; 30 hours supervised practical sessions	Online modules;8-weekcourse including theory and practical sessions	2.5-day course including theory and practical sessions; participants had previous echo training	12 – 18 months of practical experience^	Online modules; 5-day course including theory and practical sessions
RHD cases	15 definite, 34 borderline	14 definite, 43 borderline	11 definite, 32 borderline	76 definite, 122 borderline	55 definite, 47 borderline
Prevalence of any RHD	4.0%	2.8%	4.5%	N/A*	4.1%
Sensitivity (95% CI) for any RHD:	83.7 (70.7 – 91.6)	84.2 (72.1 – 92.5)	74.4 (58.8 – 86.5)	85 (80 - 90)	70.4 (62.2 – 77.8)
Specificity (95% CI) for any RHD:	90.9 (89.9 – 92.4)	85.6 (83.9 – 87.1)	78.8 (76.0 – 81.4)	65 (60 - 70)	78.1 (76.4 – 79.8)

^ Echocardiography was performed by experts; 12-18 months training relates to those who interpreted the images

*retrospective review of a selected cohort

Table 2: 2012 World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease in people aged 20 years or less (16).

Definite RHD (either A, B, C, or D): A) Pathological MR and at least two morphological features of RHD of the MV B) MS mean gradient ≥4 mmHg* C) Pathological AR and at least two morphological features of RHD of the AV‡ D) Borderline disease of both the AV and MV§
Borderline RHD (either A, B, or C): A) At least two morphological features of RHD of the MV without pathological MR or MS B) Pathological MR C) Pathological AR
Normal echocardiographic findings (all of A, B, C, and D): A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR) B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR) C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
* Congenital MV anomalies must be excluded. ‡Bicuspid AV, dilated aortic root, and hypertension must be excluded. §Combined AR and MR in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic. Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease; WHF, World Heart Federation.

Authors contributions:JRF and HF conceived the study and wrote initial drafts of the protocol; GAW, AK, APR, JY, JC, VW, AM, BR contributed to study design and reviewed and approved the written protocol; VW provided input on issues related to engagement with Aboriginal and Torres Strait Islander people; and AM provided input on issues related to engaging with Timorese people and the health system in Timor-Leste.

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Competing interests statement: None of the authors have competing interests to declare.

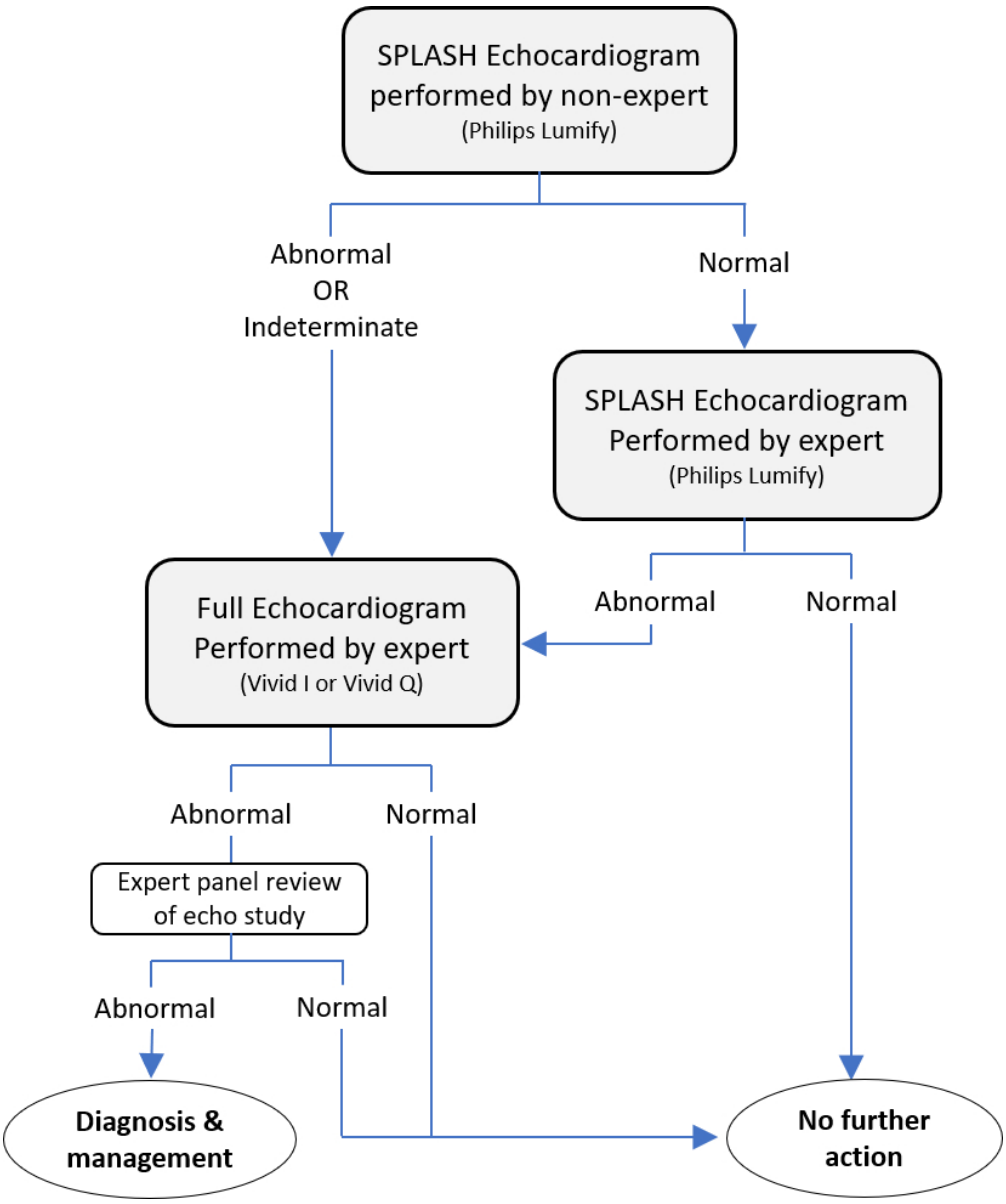

Figure 1: Flow of participants through the study

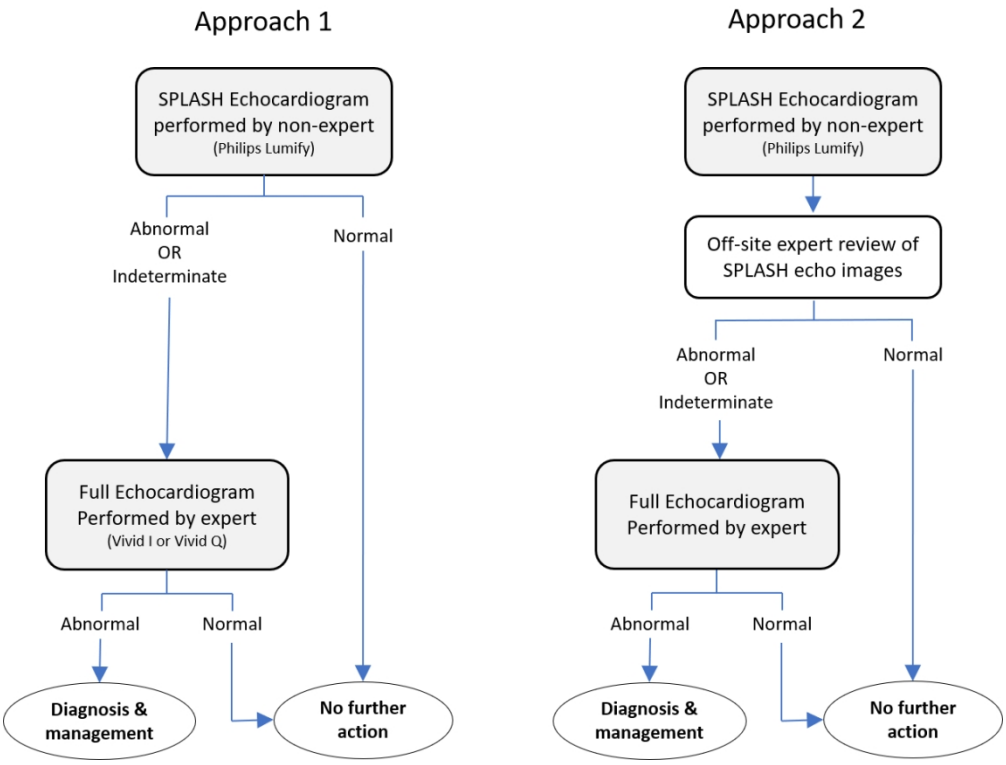

Figure 2: Illustration of Approach 1 and Approach 2

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3
	4	Study objectives and hypotheses	3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6
	11	Rationale for choosing the reference standard (if alternatives exist)	7
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	7
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/A
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/A
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	N/A
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	9
	29	Where the full study protocol can be accessed	N/A
	30	Sources of funding and other support; role of funders	16

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.